AR201-13462B

# HPV Data Set

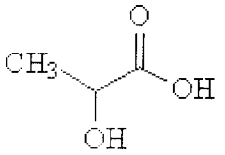
# LACTIC ACID

# CAS # 50-21-5

# Dossier number 50215

## Substance information

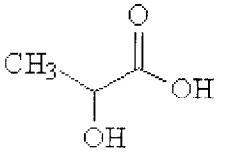
| | |
|---|---|
| **CAS No.** | 50-21-57 |
| **EINECS Name:** | lactic acid |
| **EC No.** | 200-018-0 |
| **TSCA Name:** | Propanoic acid, 2-hydroxy-, (2S)- |
| **Molecular Formula** | C3H6O3 |



| | |
|---|---|
| **IUPAC Name:** | LACTIC ACID |
| **Mol. Weight:** | 90 |
| **Physical status:** | liquid or white crystals |
| **Colour:** | colourless to slightly yellow |
| **Odour:** | nearly odourless |

**Most of the lactic acid nowadays is supplied in the L(+) form, the natural form.**
**PURAC only manufacturers the L(+) form.**
**Substance information for the L(+) lactic acid is as follows:**

| | |
|---|---|
| **CAS No.** | 79-33-4 |
| **EINECS Name:** | L(+) lactic acid |
| **EC No.** | 201-196-2 |
| **TSCA Name:** | Propanoic acid, 2-hydroxy-, (2S)- |
| **Molecular Formula** | C3H6O3 |



| | |
|---|---|
| **IUPAC Name:** | L(+) LACTIC ACID |
| **Mol. Weight:** | 90 |
| **Physical status:** | liquid or white crystals |
| **Colour:** | colourless to slightly yellow |
| **Odour:** | nearly odourless |

**This HPV data file typically contains information about L(+) lactic acid.**

# Chapter 1 Physico-chemical Data

- ***Melting Point***

| | |
|---|---|
| Value: | ≤ 54 degree C |
| Decomposition: | no at < 110 degree C |
| Sublimation: | no |
| Method: | other |
| GLP: | no data |
| Test substance: | 100% crystalline pure product used |

- **Boiling Point / Vapour pressure**

| | |
|---|---|
| Boiling point: | ca. 258 degree C at 1000 hPa |
| Vapour pressure: | ca. .0041 hPa at 20 degree C |
| Decomposition: | yes |
| Method: | other |
| GLP: | no data |
| Remark: | solutions can polymerise on boiling |

It is not possible to determine this value very accurate, because lactic acid tends to polymerise by a polycondensation reaction.
The boiling point of lactic acid at difference vapour pressures according to

- Aspen Database
- PURAC In-house Pure compound database

**Table** Boiling points of lactic acid at different pressures (Aspen Database)

| Pressure (mbar) | Boiling temperature (°C) |
|---|---|
| 1 | 79.6 |
| 5 | 101.9 |
| 10 | 112.8 |
| 50 | 141.8 |
| 100 | 156.2 |
| 200 | 172.1 |
| 400 | 189.8 |
| 600 | 201.0 |
| 800 | 209.4 |
| 1013 | 216.6 |

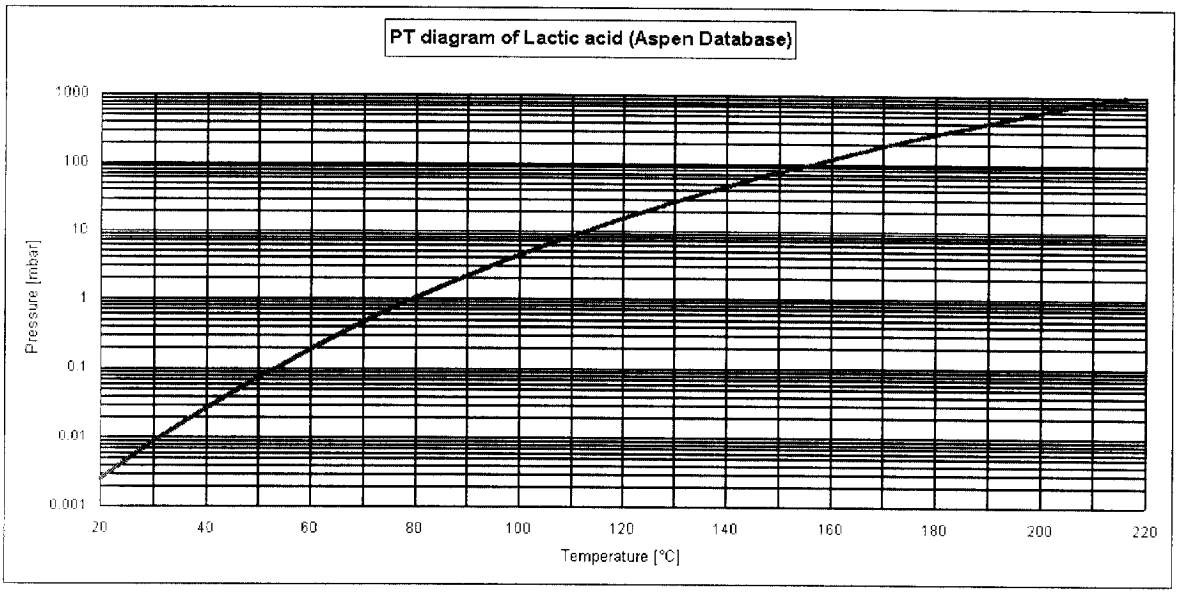
The vapour pressures of lactic acid as a function of the boiling temperature according to the Aspen formula (PLXANT).

$$PLXANT = e^{C1+\frac{C2}{C3+T}+C4*T+C5*\ln T+C6*T^{C7}}$$

: Vapour pressure ($N/m^2$ or Pa)

PLXANT
C1, C2 C3, C4, C5, C6, C7 : Regression coefficients for chemical compound
T : Boiling temperature (K)

**Figure** Vapour Pressure diagram




The regression coefficients are:

| | |
|---|---|
| C1 = 225.19 | C5 = -28.816 |
| C2 = -18757 | C6 = 0.000012998 |
| C3 = 0 | C7 = 2 |
| C4 = 0 | |

G.P.v.Lieshout measured the vapour pressure of lactic acid between 0 and 180 °C.

**Table** Boiling points of lactic acid at different pressures

| Temperature (°C) | Vapour Pressure (mbar) |
|---|---|
| 0 | 0.0005 |
| 10 | 0.0015 |
| 20 | 0.0041 |
| 30 | 0.0107 |
| 40 | 0.0258 |
| 50 | 0.0588 |
| 60 | 0.1273 |
| 70 | 0.2629 |
| 80 | 0.5198 |

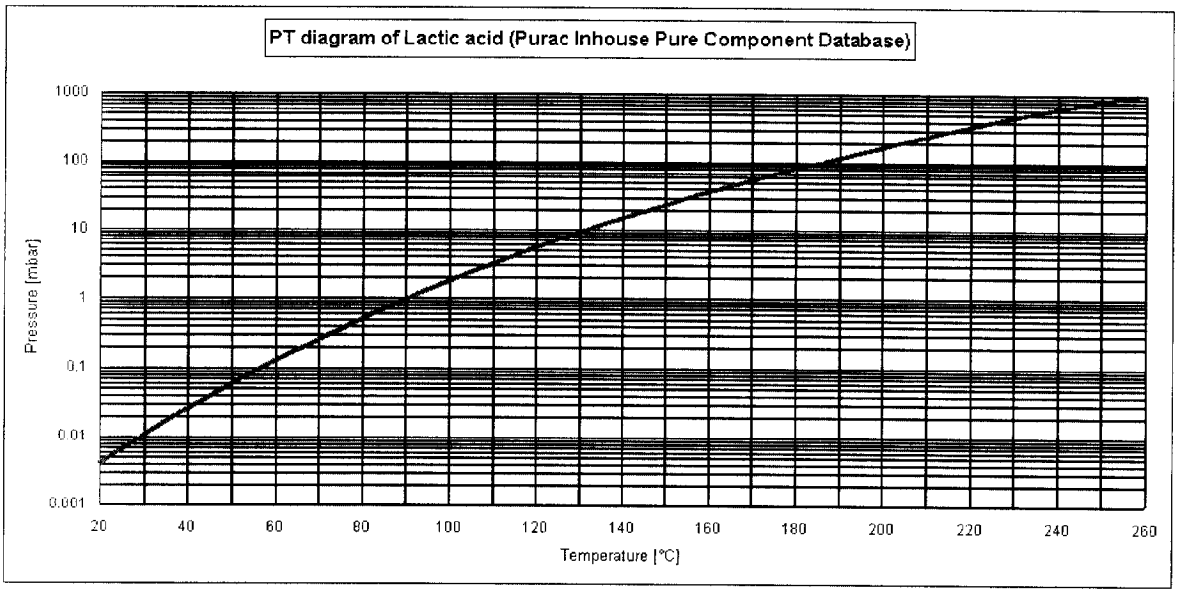
| | |
|---|---|
| 90 | 0.9877 |
| 100 | 1.8093 |
| 110 | 3.2042 |
| 120 | 5.5004 |
| 130 | 9.1736 |
| 140 | 14.8959 |
| 150 | 23.5938 |
| 160 | 36.5163 |
| 170 | 55.3114 |
| 180 | 82.1111 |

The vapour pressures of lactic acid as a function of the boiling temperature were fitted with the Aspen formula (PLXANT). The estimated atmospheric boiling point is about 258 °C.

$$PLXANT = e^{C1+\frac{C2}{C3+T}+C4*T+C5*\ln T+C6*T^{C7}}$$

PLXANT : Vapour pressure ($N/m^2$ or Pa)

C1, C2 C3, C4, C5, C6, C7 : Regression coefficients for chemical compound




T : Boiling temperature (K)

Figure: Vapour Pressure diagram

The regression coefficients are:

| | |
|---|---|
| C1 = 32.4649 | C5 = -0.376037 |
| C2 = -8835.5 | C6 = 0 |
| C3 = 0 | C7 = 0 |
| C4 = -0.003654 | |

- **Density**

| | |
|---|---|
| Type: | density |
| Value: | >= 1.2255 g/cm³ at 20 degree C |
| Method: | other |
| GLP: | yes |
| Test substance: | Lactic acid 80% |

Holten describes the liquid density of lactic acid solutions in water.
**Table** Liquid Densities of aqueous lactic acid solutions at different temperatures.

| Concentration (wt%) | Temperature (°C) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 |
| 0 | 1.0004 | 0.9997 | 0.9979 | 0.9953 | 0.9919 | 0.9878 | 0.9831 | 0.9778 | 0.9720 | 0.9658 | 0.9591 |
| 10 | 1.0269 | 1.0251 | 1.0223 | 1.0188 | 1.0145 | 1.0097 | 1.0042 | 0.9983 | 0.9919 | 0.9851 | 0.9779 |
| 20 | 1.0535 | 1.0505 | 1.0468 | 1.0424 | 1.0373 | 1.0317 | 1.0256 | 1.0190 | 1.0120 | 1.0047 | 0.9970 |
| 30 | 1.0802 | 1.0762 | 1.0715 | 1.0662 | 1.0604 | 1.0540 | 1.0472 | 1.0400 | 1.0325 | 1.0246 | 1.0164 |
| 40 | 1.1069 | 1.1019 | 1.0964 | 1.0902 | 1.0836 | 1.0766 | 1.0692 | 1.0614 | 1.0533 | 1.0449 | 1.0363 |
| 50 | 1.1333 | 1.1275 | 1.1211 | 1.1142 | 1.1069 | 1.0992 | 1.0912 | 1.0829 | 1.0743 | 1.0655 | 1.0564 |
| 60 | 1.1591 | 1.1524 | 1.1453 | 1.1377 | 1.1299 | 1.1216 | 1.1131 | 1.1043 | 1.0953 | 1.0861 | 1.0766 |
| 70 | 1.1835 | 1.1762 | 1.1685 | 1.1604 | 1.1521 | 1.1434 | 1.1345 | 1.1254 | 1.1160 | 1.1065 | 1.0967 |
| 80 | 1.2061 | 1.1983 | 1.1902 | 1.1818 | 1.1731 | 1.1642 | 1.1550 | 1.1456 | 1.1360 | 1.1263 | 1.1163 |
| 90 | 1.2263 | 1.2183 | 1.2100 | 1.2014 | 1.1925 | 1.1834 | 1.1741 | 1.1646 | 1.1550 | 1.1451 | 1.1351 |
| 95 | 1.2354 | 1.2274 | 1.2190 | 1.2104 | 1.2015 | 1.1924 | 1.1831 | 1.1736 | 1.1639 | 1.1541 | 1.1441 |
| 100 | 1.2438 | 1.2357 | 1.2274 | 1.2188 | 1.2099 | 1.2008 | 1.1916 | 1.1821 | 1.1725 | 1.1627 | 1.1527 |

**Liquid Density of <u>pure lactic acid</u>**

The liquid density of pure lactic acid at difference temperatures according to:

- Aspen Database
- PURAC In-house Pure Component Database

**Table** Densities of lactic acid at different temperatures (ASPEN Database)

| Temperature (°C) | Density (g/ml) |
|---|---|
| 20 | 1.2255 |
| 30 | 1.2163 |
| 40 | 1.2069 |
| 50 | 1.1974 |
| 60 | 1.1878 |
| 70 | 1.1780 |
| 80 | 1.1681 |
| 90 | 1.1580 |
| 100 | 1.1478 |
| 110 | 1.1374 |
| 120 | 1.1268 |
| 130 | 1.1160 |
| 140 | 1.1051 |
| 150 | 1.0939 |
| 160 | 1.0825 |

The liquid densities of lactic acid as a function of the temperature according to the Aspen equation for liquid density (DNLDIP):

$$DNLDIP = \frac{C1}{C2^{1+(1-\frac{T}{C3})^{C4}}}$$

DNLDIP : Liquid density (kmole/$m^3$)
C1, C2 C4 : Regression coefficients for chemical compound
C3 : Critical temperature (K)
T : Temperature (K)
The regression coefficients are:
C1 = 0.9798 C3 = 675
C2 = 0.24593 C4 = 0.2333

**Liquid density diagram**

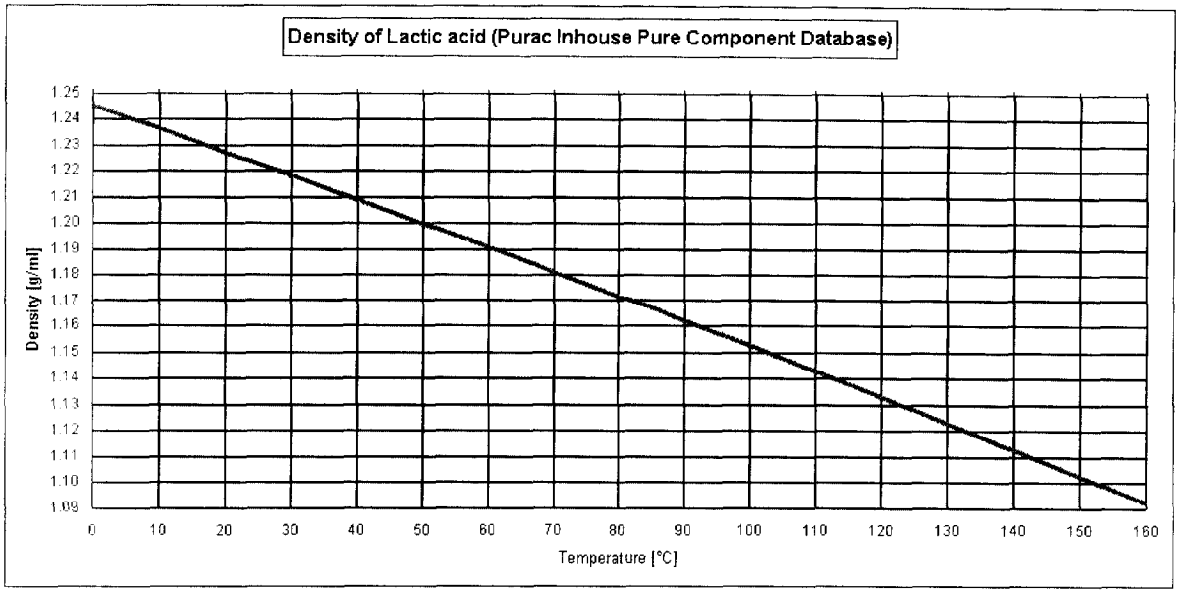



**Table** Densities of lactic acid at different temperatures (Purac In-house Pure Component Database)

| Temperature (°C) | Density (g/ml) |
|---|---|
| 0 | 1.2453 |
| 10 | 1.2364 |
| 20 | 1.2274 |
| 30 | 1.2183 |
| 40 | 1.2092 |
| 50 | 1.2000 |
| 60 | 1.1907 |
| 70 | 1.1813 |
| 80 | 1.1719 |
| 90 | 1.1623 |
| 100 | 1.1527 |
| 110 | 1.1429 |
| 120 | 1.1330 |
| 130 | 1.1231 |
| 140 | 1.1130 |
| 150 | 1.1028 |
| 160 | 1.0924 |

The liquid densities of lactic acid as a function of the temperature according to the Aspen equation for liquid density (DNLDIP):

$$DNLDIP = \frac{C1}{C2^{1+(1-\frac{T}{C3})^{C4}}}$$

DNLDIP : Liquid density (kmole/$m^3$)

C1, C2 C4 : Regression coefficients for chemical compound
C3 : Critical temperature (K)
T : Temperature (K)
The regression coefficients are:
C1 = 1.61248 C3 = 729.9
C2 = 0.314479 C4 = 0.328317

- ***Partition Coefficient***

Partition Coeff.: octanol-water
log Pow: ca. -.62 at 20 degree C
Method: OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year: 1987
GLP: yes

- ***Solubility in water***

Value: ca. 100 vol% at 25 degree C
pH value: ca. 1.2
pKa: 3.68 at 25 degree C
Descr.: of very high solubility
Method: other
GLP: no data
Deg. product: not measured
Stable: yes
Remark: completely soluble at 25 degrees C

J.v.Krieken determined the phase diagram of lactic acid/ water. Due to practical problems the diagram wasn't completed, but the missing part was extrapolated.

**Table** Solubility of monomeric lactic acid in water

| Temperature (°C) | Lactic acid (wt%) |
|---|---|
| -20 | 65.9 |
| -15 | 68.8 |
| -10 | 71.5 |
| -5 | 74.2 |
| 0 | 76.7 |
| 5 | 78.6 |
| 10 | 81.3 |
| 15 | 83.5 |
| 20 | 86.1 |
| 25 | 87.6 |
| 35 | 92.7 |
| 40 | 95.1 |

**Table** Freezing point data of monomeric lactic acid in water

| Temperature (°C) | Lactic acid (wt%) |
|---|---|

| | |
|---|---|
| 0 | 0 |
| -5 | 18.6 |
| -10 | 32.5 |
| -15 | 41.9 |
| -21 | 51.7 |

The eutectic point of lactic acid/water was calculated by extrapolation and is ca. 61.7 wt% lactic acid and -27.1 °C.

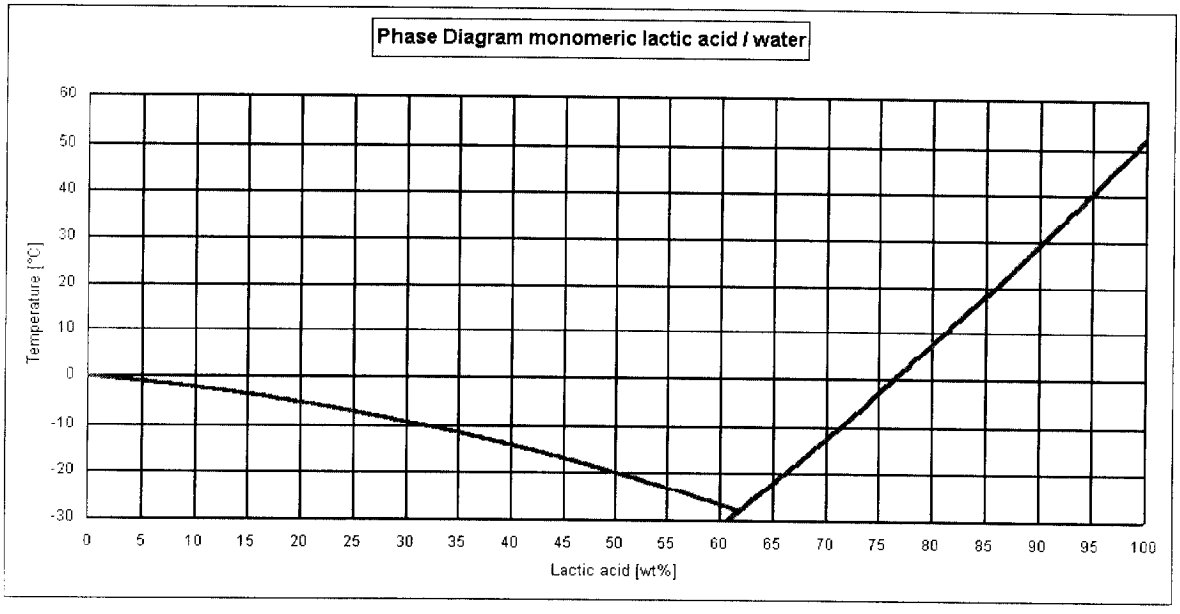



**Figure** Phase Diagram

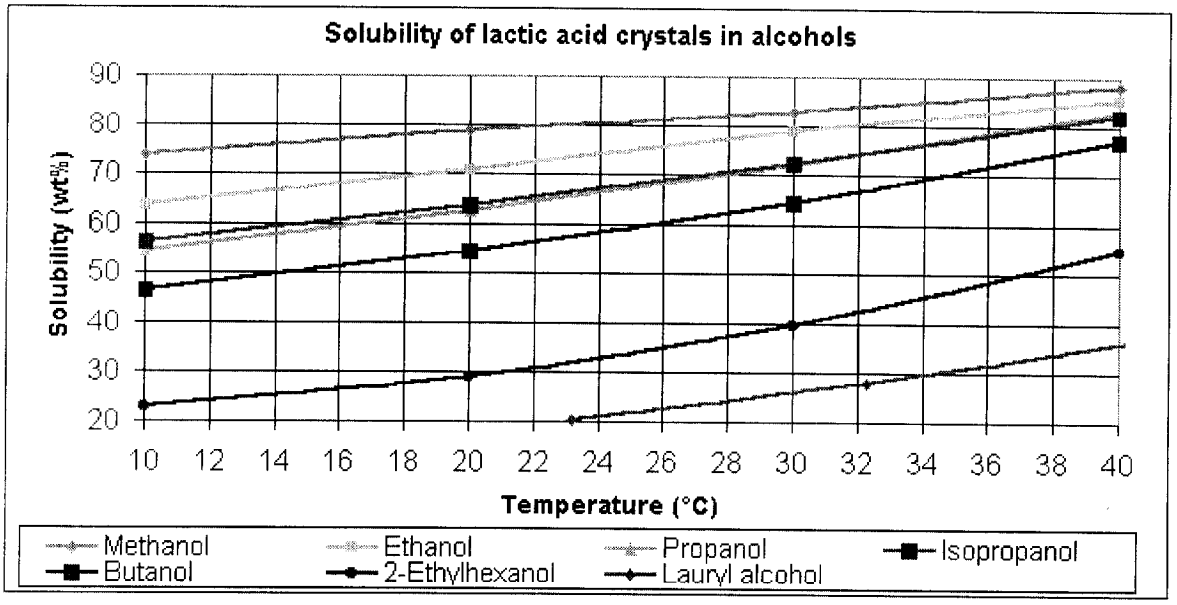
### Solubility of lactic acid in other solvents

J.v. Krieken investigated the solubility of pure lactic acid in a range of solvents by stirring the specific solvent with an excess of (S)-lactic acid crystals at a specific temperature. After separation of the solids from the liquid, the clear liquid was analysed on free acidity.

**Table** solubility of lactic acid in a range of solvents

| Solvent | Solubility (wt%) of solution | | | |
|---|---|---|---|---|
| | 10°C | 20°C | 30°C | 40°C |
| Methanol | 73.8 | 78.6 | 82.8 | 88.1 |
| Ethanol | 63.6 | 70.9 | 78.7 | 85.2 |
| 1-Propanol | 54.5 | 62.4 | 71.7 | 82.7 |
| 2-Propanol | 56.1 | 63.4 | 72.2 | 82.2 |
| 1-Butanol | 46.3 | 54.5 | 64.3 | 77.1 |
| 2-Ethyl-1-hexanol | 22.9 | 29.0 | 39.6 | 54.9 |
| Cyclohexane | | | | 0.04 |
| Hexane | < 0.01 | < 0.01 | < 0.01 | 0.02 |

| | | | | |
|---|---|---|---|---|
| Toluene | 0.06 | 0.11 | 0.24 | 0.50 |
| Ethyl lactate | 37.0 | 45.9 | 57.2 | 72.8 |
| Butyl lactate | 27.7 | 35.7 | 47.3 | 64.8 |
| 2-Ethylhexyl lactate | 15.5 | 20.9 | 30.9 | 46.7 |
| Ethyl acetate | 27.1 | 39.9 | 56.2 | 72.9 |
| Diethyl ether | 23.8 | 38.7 | 59.8 | |
| Diisopropyl ether | 6.4 | 9.2 | 15.9 | 44.4 |
| Tetrahydrofuran | 58.4 | 65.1 | 72.4 | 82.9 |
| Dichloromethane | 0.59 | 1.02 | 2.7 | |
| Chloroform | 0.31 | 0.67 | 1.67 | 59.7 |
| 2-Butanone | 40.7 | 52.9 | 67.3 | 81.6 |
| Acetone | 53.4 | 61.4 | 71.5 | 82.9 |




- ***Viscosity***

Test type: other: ASPEN database ; PURAC internal
Value: ca. 53.52 mPa s (dynamic) at 20 degree C

The liquid viscosity of lactic acid at difference temperatures according to

- Aspen Database
- PURAC In-house Pure Component Database

The liquid viscosity of aqueous lactic acid solutions in water

- 0 - 88 wt% of Lactic Acid
- 90 - 110 wt% Lactic Acid

**Table** Viscosity of lactic acid at different temperatures (Aspen Database)

| Temperature (°C) | Viscosity (cP) |
|---|---|
| 20 | 53.52 |
| 30 | 33.26 |
| 40 | 21.29 |
| 50 | 14.01 |
| 60 | 9.44 |
| 70 | 6.51 |
| 80 | 4.59 |
| 90 | 3.29 |
| 100 | 2.40 |
| 110 | 1.78 |
| 120 | 1.34 |
| 130 | 1.03 |
| 140 | 0.79 |
| 150 | 0.62 |
| 160 | 0.49 |

The liquid viscosity of lactic acid as a function of the temperature according to the Aspen equation for liquid viscosity (MULDIP):

$$MULDIP = e^{C1+\frac{C2}{T}+C3*\ln T+C4*T^{C5}}$$

MULDIP : Liquid viscosity ($N*s/m^2$ or Pa.s)
C1, C2 C3, C4, C5 : Regression coefficients for chemical compound
T : Temperature (K)

The regression coefficients are:
C1 = -14.403
C2 = 4097.9
C3 = -0.4407
C4 = 0
C5 = 0

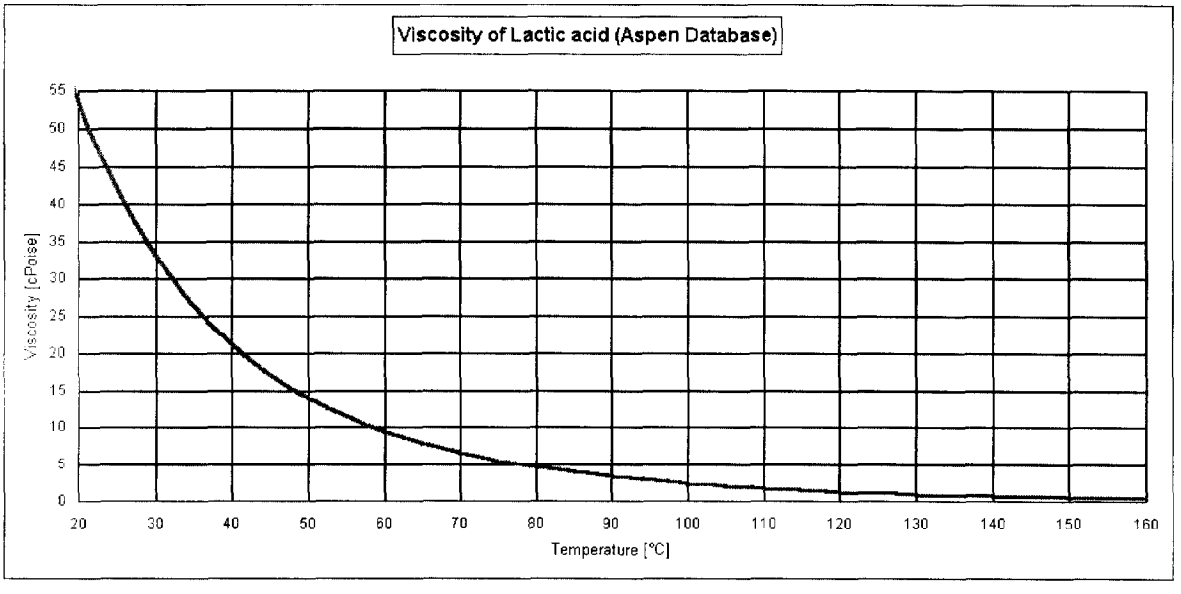


**Figure**: Liquid Viscosity diagram

Table 12 Viscosity of lactic acid at different temperatures (Purac In-house Pure Component Database) [2]

| Temperature (°C) | Viscosity (cP) |
|---|---|
| 20 | 1342.33 |
| 30 | 579.14 |
| 40 | 280.59 |
| 50 | 150.73 |
| 60 | 88.80 |
| 70 | 56.81 |
| 80 | 39.14 |
| 90 | 28.83 |
| 100 | 22.54 |

The liquid viscosity of lactic acid as a function of the temperature according to the Aspen equation for liquid viscosity (MULDIP):

MULDIP: Liquid viscosity ($N*s/m^2$ or Pa.s)
C1, C2, C3, C4, C5: Regression coefficients for chemical compound
T: Temperature (K)

The regression coefficients are:

C1: 421.094
C2: 25091.4
C3: 59.1119
C4: 0
C5: 0

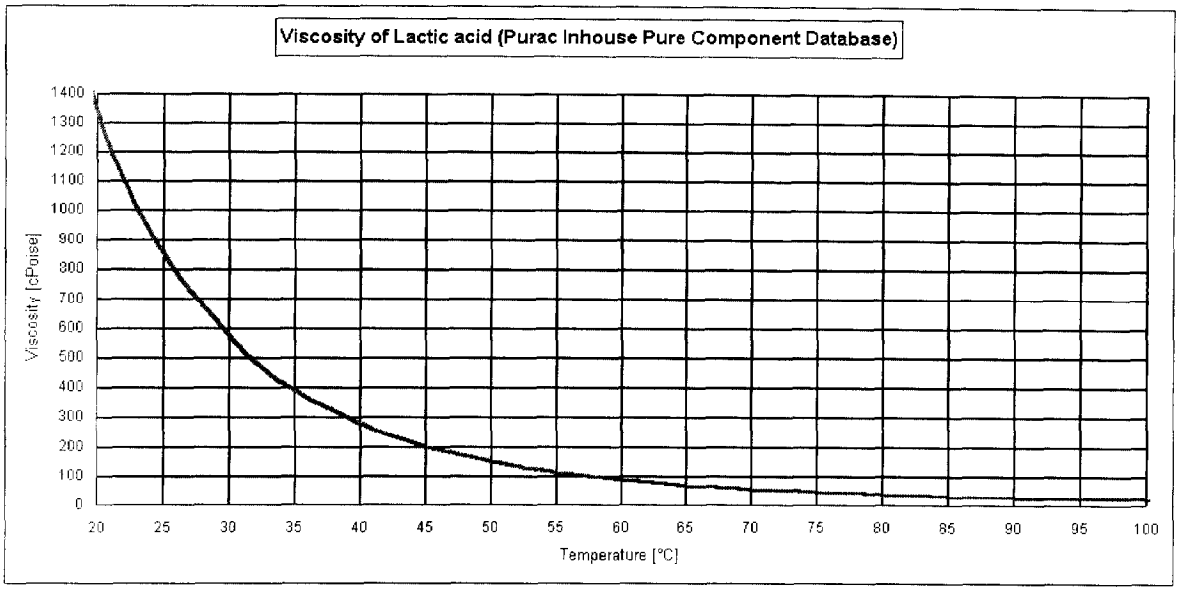



**Figure**: Liquid Viscosity diagram

## *References Chapter 1: Physico chemical data*


- National Chemical Inventories
  Coden NCINF5
  ISSN: 1089-6279

- Handbook of Chemistry and Physics
  WEAST
  66th Edition

- ASPEN database

- PURAC internal databank

# Chapter 2 Environmental Fate and Pathways

- ***Photodegradation***

The photochemical oxidisation of lactic acid is discussed in "Lactic acid properties and chemistry of lactic acid and derivatives by C.H. Holten (1971)". The first observation that lactic acid is photosensitive was made in 1910 by Berthelot and Gaudechon, who irradiated calcium lactate and ethyl lactate with ultraviolet rays. They observed decomposition with the formation of gas containing carbon monoxide, carbon dioxide, hydrogen and methane.

- ***Stability in Water***

Lactic Acid (88% and 60% aqueous solutions) were investigated.
"The kinetics of degradation of Lactic Acid was done at elevated temperature, since the decomposition rates of lactic acid, (..) were too slow to obtain kinetic data within reasonable time. At the condition studied (25, 40, 80 and 120 degrees centigrade) the decompositions of these compounds followed apparent first order kinetics because the mean correlation coefficient was above 0.980.
Lactic acid was very stable in aqueous solutions at 80 degrees centigrade (less than 30% decomposition after 175 at 80 degrees) and degradation was not different when combined with the various excipients tested. The shelf lives determined for lactic acid ranged from 79 years when combined with isopropyl palmitate to 98 years when combined with sorbic acid.

- ***Transport between Environmental Compartments***

Type: other: see free texts RM.
Remark: Lactic acid is not volatile and it has a high biodegradation rate. Therefor transport between compartments is no issue for this compound.
Biodegradation

Value 50% after 5 days and 67% after 20 days.
Breakdown Product: L(+) lactic acid 80%
Method: BOD (Biochemical Oxygen Demand) and COD (Chemical Oxygen Demand) determinations were carried out for L(+) lactic acid usig the method described in teh Dutch guidenlines "water determination of biochemical oxgen demand after n days (BODn)" (NEN 6634) and "Water determination of chemical oxygen demand (COD" (NEN 6633) respectively, these methods are similar to those referred in the EC Test Guidelines C.8 and C.9 Two concentrations (2 mg/L and 4 mg/L) were tested.
An oculum was prepared from activated sludge. Its microbial activity appeared to be sufficient although the control substance glucose and glutamic acid had a BOD5 of slightly less than the required value of 4.00 ± 0.75 mg $O_2$/L

## *References Chapter 2: Environmental fate and pathways*

- Lactic Acid: properties and chemistry of lactic acid and derivatives by C.H. Holten,

1971, page 38

- TNO report R 92/018: BOD and COd of L(+) lactic acid according to EC test guidelines C.8 and C.9

- The ecotoxicity and the biodegradability of lactic acid, alkyl esters and lactate salts
  C.T. Bowmer et.al.
  Chemosphere, volume 37, No 7, pp 1317 - 1333, 1998

- Stability of lactic acid and glycolic acid in aqueous systems subjected to acid hydrolysis and thermal decomposition.
  M.M. de Villiers et.al.
  Journal of the society of cosmetic chemists, 48, 165-174 (August 1998)

- Handbook of Chemistry and Physics
  WEAST
  66th Edition

# Chapter 3 Ecotoxicity

- ***Acute/Prolonged Toxicity to Fish***

- Type: semistatic
  Species: Brachydanio rerio (Fish, fresh water)
  Exposure period: 48 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  LC50: = 320 - calculated
  Limit Test: no
  Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
  Year: 1992
  GLP: yes
  Test substance: 80% L(+) Lactic Acid

- Type: semistatic
  Species: Brachydanio rerio (Fish, fresh water)
  Exposure period: 96 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 320 - measured/nominal
  LC50: = 320 - calculated
  LC100: = 560 - calculated
  Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
  Year: 1982
  GLP: yes
  Test substance: 88% L(+) Lactic Acid
  Remark: test solutions are not neutralised. It is more than likely that the low pH value affected the survival of the fishes.

- Type: static
  Species: Lepomis macrochirus (Fish, fresh water)
  Exposure period: 96 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 56 - measured/nominal
  LC50: = 130 - measured/nominal
  LC50 24h : = 140 - measured/nominal
  LC50 48h : = 130 - measured/nominal
  Limit Test: yes
  Method: :
  The study was conducted at the concentrations of 56; 100, 180; 320 and 560 mg/l. Ten fish with a mean weight of 0.37 g and a mean standard length of 24 mm, were exposed to each test concentration and control.
  The procedures for static bioassay described in (1) and (2) below were used in this experiment.
  (1) Committee on methods for Toxicity Tests with Aquatic Organisms (C.E. Stephan chairman). 1975. Methods for acute toxicity tests with fish, macro invertebrates and

amphibians.
Environmental Protection Agency, Ecological Research Series EPA 660/3-75-009, April 1975; 61p

(2) American Public Health Association. 1980. Standard methods for the examination of water and wastewater. 15th ed. Washington DC 1134p.
Year: 1984
GLP: yes
Test substance: 88% L(+) Lactic Acid
Conclusion:
The results of the four day static fish toxicity studies indicated a 96h LC50 of 103 (100 - 180) mg/l and a No-Observed-Effect Concentration of 56 mg/l. Abnormal effects of mortality and / or surfacing were observed during the 96 hour exposure period. The 24h LC50 was 140 mg/l and the 48h LC50 was 130 mg/l.

- Type: static
  Species: Salmo gairdneri (Fish, estuary, fresh water)
  Exposure period: 96 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 56 - measured/nominal
  LC50: = 130 - measured/nominal
  LC50 24h : = 150 - measured/nominal
  LC50 48h : = 130 - measured/nominal
  Method:
  The static fish bioassay was conducted in five gallon glass vessels containing 15 litres reconstituted water. The study was conducted at the nominal concentrations of 32, 56, 100,180 and 320 mg/l. Ten fish were exposed to each test concentration and control.
  Conclusion:
  The results of the four day static fish toxicity studies using test substance are summarised below:
  24-hour LC50 150 mg/l
  48-hour LC50 130 mg/l
  96-hour LC50 130 (100 - 180) mg/l
  96-hour NOEC 56 mg/l

- ***Acute Toxicity to Aquatic Invertebrates***

- Type: static
  Species: Daphnia magna (Crustacea)
  Exposure period: 48 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 180 - calculated
  EC50: = 240 - calculated
  EC100: = 320 - calculated
  EC 50 24h : = 240 - calculated
  Limit Test: no
  Method: OECD Guide-line 202
  Year: 1992

GLP: yes
Test substance: 80% L(+) Lactic Acid
Remark:
test solutions are not neutralised. It is more than likely that the low pH values affected the mobility of the daphnia's.

- Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l
Analytical monitoring: yes
NOEC: = 320 - measured/nominal
LC50 48h : = 750 - measured/nominal
Limit Test: yes
Method:

Five concentrations in duplicate of the test compound with ten Daphnia per 250 ml glass beaker were used. The concentrations were a logarithmic series ranging from 100 to 1000 mg/l and included a control. The procedure for static bioassay as described in (1) and (2) below were used.

(1) Methods of acute toxicity with fish, Macro invertebrates and Amphibians. Stephan, CE, chairman. 1975.
Committee on Methods for toxicity tests with aquatic organisms. US EPA Ecol. Res. Ser. 660/3-75009.
(2) American Public Health Association. 1980. Standard methods for the examination of Water and wastewater. 15th ed. Washington DC. 1134p.
Year 1984
GLP: yes
Test substance: 88% L(+) Lactic Acid

- ***Toxicity to Aquatic Plants e.g. Algae***

- Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 70 hour(s)
Unit: g/l
Analytical monitoring: yes
NOEC: = 1.9 - calculated
EC10: = 2.3 - calculated
EC50: = 3.5 - calculated
EC90 : = 5.4 - calculated
Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1982
GLP: yes
Test substance: 80% L(+) neutralised L(+) lactic acid

- ***Toxicity to Micro-organisms e.g. Bacteria***

- Type: other: laboratory incubations
  Species: Escherichia coli (Bacteria)
  Exposure period: 20 minute(s)
  Unit: g/l
  EC100 : = 15 - measured/nominal
  Test substance`: combinations of 1.0-1.5% lactic acid with 0.1% sodium benzoate, or 0.1% hydrogen peroxide, or 0.005% glycerol monolaurate.
  Result:
  At 22C complete inactivation of E. coli O157:H7 was observed after 20 min. of exposure to 1.5% lactic acid plus 0.1% hydrogen peroxide.
  Conclusion:
  The mentioned treatment could potentially be used to inactivate or reduce E. coli O157:H7 populations on raw products

- Type: other: laboratory incubations on lean beef muscle discs
  Species: other bacteria: Listeria monoccytogenes, Yersinia enterocolitica, Salmonella typhimurium, E.coli, Campylobacter jejuni, Staphylococcus aureus, Pseudomonas fragi, Brochotrix thermosphacta.
  Exposure period: 0 minute(s)
  Remark: Acid temperature (20 & 50 C) and concentration (1%, 3%) and initial numbers of contaminating bacteria (log CFU/cm2 of 3-6) were the variables studied.
  Result: The bactericidal efficacy of lactic acid was often distinct for each organism. Bacterial numbers were maximally reduced with 3% acid at 55C. S.aureus: 1.4 log cycle; P. fragi: 2.3 log cycle; B. thermosphacta: 2.8 log cycle reduction.

## *References Chapter 3: Ecotoxicity*

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  Analytical Biochemistry Laboratories Inc.
  Columbia, MO
  1984

- Acute toxicity of L(+) lactic acid to Bluegill Sunfish (Lepomis macrochirus)
  Analytical Biochemistry Laboratories Inc.
  Columbia, MO
  1984


- Acute toxicity to aquatic invertebrates

- TNO-report R 91/ 294; The acute toxicity of L(+)-lactic acid to Daphnia Magna (OECD 202, 48h).

- Acute toxicity of L(+) lactic acid to Daphnia Magna
  Analytical Biochemistry Laboratories Inc.
  Columbia, MO
  1984

▪ Toxicity to aquatic plants e.g. algae

- TNO report R 92/009 ; Effect of L(+)-lactic acid on the growth of the alga Selenastrum Capricornutum (OECD 201).

▪ Toxicity to micro-organisms e.g. bacteria

- Food Microbiology 16: 75-82 (1999), Venkitanarayanan K.S.,
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  Food Research International 25: 355-362 (1992).

# Chapter 4 Mammalian toxicity

- ***Toxicokinetics, Metabolism and Distribution***

- In Vitro/in vivo: In vivo
  Type: Metabolism
  Species: mammal
  Remark:

  (L)-lactic acid is a natural functional metabolite in mammal, as mammalian fuel. According to the lactate shuttle concept, L-lactate represents a major means of distributing carbohydrate potential energy for oxidation and gluconeogenesis. The concept of a "lactate shuttle" (Brooks, 1998) is that during hard exercise, as well as other conditions of accelerated glycolysis, glycolic flux in muscle involves L-lactate formation regardless of the state of oxygenation. The production rate of endogenous (L)-lactate in the resting human is about 1.3 mol (70 kg/bw).24 h-1 (= 117 g/day).

- ***Acute oral toxicity***

- LD50
  Species: rat
  Strain: Charles River
  Sex: male/female
  No. of Animals: 55
  Doses: 3,162 / 3,548 / 3,981 / 4,467 / 5,012 / 5,623 / 6,310 mg /kg bw
  $LD_{50}$: between 3543 and 4936 mg/kg bw
  Method: EPA OPP 81-1
  Year: 1984
  GLP: yes
  Test substance: L(+) lactic acid 80%

- LD100
  Species: rat
  No. of Animals: 10
  Vehicle: water
  Doses: dose was daily increased: 0.25 ml till 4.5 ml lactic acid 50%
  $LD_{100}$: = 11250 mg/kg bw
  Test substance: L(+) lactic acid 80%
  Remark:
  2 Rats died after dosing with 3 ml = 7500 mg/kg bw. The animals had a 15% reduction in bw in 1 week. A single administration of large doses did not result in changes in carbon dioxide content or pH of the blood, but a considerable decrease in the pH of the urine.

- Single dose toxicity
  Species: rat

| | |
|---|---|
| Strain: | Charles River |
| Sex: | male/female |
| No. of Animals: | 10 |
| Doses: | 5 mg / kg bodyweight |
| Method: | EPA OPP 81-1 |
| Year: | 1983 |
| GLP: | yes |
| Test substance: | L(+) lactic acid 80% |

Remark:
Test was done to establish clinical signs after single dose treatment
Conclusion:
Four males survived the 14-day duration of the study. One male and all females were found dead on the day of dosing (day 0), on day 1 or on day 10. No abnormal clinical signs were observed during the study.

- ***Acute Inhalation Toxicity***

| | |
|---|---|
| - Type: | other: Acute inhalation toxicity study |
| Species: | rat |
| Strain: | Fischer 344 |
| Sex: | male/female |
| No. of Animals: | 10 |
| Vehicle: | other: aerosol |
| Doses: | 7,94 mg/L (air) |
| Exposure time: | 4 hour(s) |
| Method: | EPA OPP 81-3 |
| Year: | 1987 |
| GLP: | yes |
| Test substance: | L(+) lactic acid 80% |

Conclusion:
Rapid breathing and eye tearing were observed during exposure. One rat from the treated group died on day 9. All other animals survived until the end of the study. Based on these results, the LC50 for L(+)Lactic Acid is greater than 7,94 mg/L.

- ***Acute Dermal Toxicity***

| | |
|---|---|
| - Type: | LD50 |
| Species: | rabbit |
| Value: | > 2000 mg/kg bw |
| Method: | OECD Guide-line 402 "Acute dermal Toxicity" |

| | |
|---|---|
| - Type: | other: Acute dermal toxicity |
| Species: | rabbit |
| Strain: | New Zealand white |
| Sex: | male/female |
| No. of Animals: | 10 |
| Doses: | 2 g/kg |
| Method: | EPA OPP 81-2 |
| Year: | 1983 |
| GLP: | yes |

Test substance: L(+) lactic acid 80%
Conclusion: All animals survived the 14-days duration of the study and gained body weight. No abnormal clinical signs were observed during the study. Severe erythema and severe oedema were observed at the test sites of all animals after removal on day 1. Erythema decreased in severity for 3 animals on day 12 or 14, and was not observed for one female on day 14.
Oedema decreased in severity for 8 animals and was not observed for one female on day 12 and for one male on day 14. Other dermal reactions observed at test sites included: blanching, necrosis, eschar formation, atonia, desquamation and denuded areas.

- ***Skin Irritation***

- Species: rabbit
Concentration: 88 %
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 12
Result: corrosive
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: 1981
GLP: yes
Test substance: L(+) lactic acid 88%
Remark:
Other studies have shown that the skin of albino rabbit is not the appropriate animal model when addressing the effects of lactic acid on human skin. This result is therefore not used for the classification.

- Species: rabbit
Concentration: 80 %
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 3
Result: not irritating
Method: OECD Guideline 404 "Acute Dermal Irritation/Corrosion"
Year 1992
GLP: yes
Test substance: buffered lactic acid: BF S36 (38% l.a. + 38% sodium lactate, total 76% d.s.). BF S30 (60% l.a. + 20% sodium lactate, total 80% d.s.)
Remark: When lactic acid is mixed with sodium lactate (buffered to pH 3.0 or 3.6), also in albino rabbits, all skin irritation scores are 0-0.
Test substance: two types of buffered lactic acid were tested: Purac BF S36 (buffered with Sodium hydroxide to pH 3.6) and Purac BF S30 (buffered with sodium hydroxide to pH 3.0)

- Species: rabbit
Exposure: Occlusive
Exposure Time: 24 hour(s)

No. of Animals: 6
Vehicle: other: not applicable
Result: highly irritating
Method: EPA OPP 81-5
Year: 1983
GLP: yes
Test substance: L(+) lactic acid 80%
Conclusion: The observations ranged from: Severe erythema, blanching and yellow-brown colour of the skin, red exudate and skin missing.
No abnormal clinical signs were observed and no mortalities occurred prior to sacrifice after the 30- to 60 minutes.
Under the definition of CFR 49, 173.136, the product does not need to be classified.

- Species: guinea pig
Concentration: 88 %
Exposure: Occlusive
Exposure Time: 4 hour(s)
Result: not irritating
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: 1981
GLP: yes
Test substance: L(+) lactic acid 88%

- Species pig
Concentration: L(+) lactic acid 88 %
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 3
|Result: not irritating
Method: both OECD Guideline 404 (1981) and Directive 84-449 B4
Year: 1981
GLP: yes
Remark: TNO believes the pig to be a more appropriate and representative animal model than the albino rabbit, when addressing the effects of lactic acid on human skin.

- ***Eye Irritation***

- Species: rabbit
Concentration: 20 % L(+) lactic acid
Vehicle: water
Result: irritating
Method: Journal Officiel de la Republique Francaise procedure; eyes were examined after 1 and 24 h and after 2, 3, 4, and 7 days with fluorescent staining.
Year: 1973
GLP: yes
Result: In same study also 50% sodium lactate was tested,

which is not irritating. Instilled at 20% and 10% provoked significant ocular irritation :Acute Ocular Irritation Index (AOII) was 39.50 resp. 31.17. Only for the 10% dilution these lesions were reversible, 7 days after instillation.

- Species: hen
  Concentration: 88 %
  Dose: 0.03 ml
  Exposure Time: 17 minute(s)
  Comment: rinsed after
  No. of Animals: 4
  Vehicle: none
  Result: highly irritating
  Method: chicken unucleated test
  Year: 1996
  GLP: yes
  Test substance: 88% L(+) Lactic acid aqueous solution

- Species: hen
  Concentration: 73 %
  Dose: 0.03 ml
  Exposure Time: .17 minute(s)
  Comment: rinsed after (see exposure time)
  No. of Animals: 4
  Vehicle: L(+) Lactic acid buffered (pH 3.6) with Sodium Lactate
  Result: highly irritating
  Method: Chicken enucleated eye test
  Year: 1996
  GLP: yes
  Test substance: 73 - 84 % L(+) Lactic acid buffered

- Species: other
  Concentration: 85 %
  Vehicle: other
  Result: irritating
  Only formulation with pH 2.02 (face cream with 11.8% lactic acid 85%) was moderate severe irritant. The formulations with pH ≥ 5.3 were minimal irritant.
  Test condition: in vitro using the Eytex Assay (Avon Products, Inc, 1995). Most of the formulations were tested undiluted. pH of formulations varies from 7.52 to 2.02.

- ***Sensitisation***

- Type: Buehler Test
  Species: guinea pig
  Concentration 1st: Induction 88 % active substance occlusive epicutaneous
  2nd: Induction 25 % active substance occlusive epicutaneous
  3rd: Challenge 88 % active substance occlusive epicutaneous
  No. of Animals: 10
  Vehicle: water
  Result: not sensitising
  Classification: not sensitising

Method: EPA OPP 81-6
Year: 1986
GLP: yes
Test substance: L()+ lactic acid 88%
Conclusion: The reactions seen (very slight to moderate erythema, very slight to moderate oedema) were considered to be irritant reactions, not sensitive reactions. The test article was not considered to be a dermal sensitiser.

- Type: Guinea pig maximisation test
Species: guinea pig
Result: not sensitising
Classification: not sensitising

- ***Repeated Dose Toxicity***

- Type: Sub-chronic
Species: rat
Route of administration: gavage
Exposure period: 90 days
Frequency of treatment: every day
Doses: 4 ml lactic acid 10% on 20 g of meal
Control Group: yes, concurrent no treatment
Result: No differences in appearance, gross observations at necropsy, or organ weights were observed between the test and control animals. Changes in blood carbon dioxide were slight.

- Type: Sub-chronic
Species: rat
Sex: female
Strain: Sprague-Dawley
Route of administration: dermal
Exposure period: 13 weeks
Frequency of treatment: daily, 5 days/week
Doses: 886 mg/kg bw
Control Group: yes, concurrent no treatment
LOAEL: 886 mg/kg
Result: No significant gross observations, with the exception of minimal skin irritation. Absolute brain weight and kidney-to-body weight ratios were increased for test animals. No lesions were observed at necropsy or at microscopic examination.
Conclusion: formulation (face cream containing 0.25% of lactic acid 85%) is safe in terms of cumulative toxicity. Based upon the exaggerated dose level used in this study for skin care products, dermal application is not likely to produce adverse effects under conditions of consumer use.

- Type: Sub-chronic
Species: rat
Sex: male/female
Strain: Fischer 344
Route of administration: experiment I: calcium lactate dissolved in drinking water

(up to 5%).

experiment II: up to 30% calcium lactate in diet.
Exposure period: 13 weeks
Frequency of treatment: daily
Test substance: Calcium lactate as a salt of lactic acid.
Doses: 5, 2.5, 1.25, 0.6, 0.3 %
Control Group: yes, concurrent no treatment
Remark: Lactic acid tested as its Calcium salt. From this study the lactate part is relevant, should be separated from effects of the soluble Calcium intake.
Result: a <10 % decrease in body weight gain. all animals survived. some haematological and biochemical parameters changed, but no severe lesions were found in microscopic examination in the experiment with ca-lactate mixed in the diet, the amount of calcium in the urine was significantly increased. Nephrocalcinosis and degeneration in kidneys observed. Indications that Nephrocalcinosis was dependent on the low Ca/Phosphorus ratio of the synthetic diet.

- Type: Sub-chronic
Species: Syrian hamster
Sex: male/female
Route of administration: other: Group 1 (control):Diet 1, contains 20% sucrose as carcinogenic diet; pure water to drink. Group 2: diet 1, mixed with 0.057 ml lactic acid 80%; pure water to drink. Group 3: same diet 1, but water containing 0.050% v/v lactic acid
Exposure period: 14 weeks
Frequency of treatment: daily ad libitum; animals of groups 2 & 3 ingest same amount lactic acid.
Post exposure period: sacrificed and autopsy; also oral cavity (caries incidence)
Control Group: yes, concurrent no treatment
Remark: pH of diet 1 is 5.55, of diet 2 is 5.12. pH of pure water is 6.8 and of water + lactic acid is 3.1 .
Result: three groups same growth and health. No significant differences were found in the incidence or extent of carious lesions among the three groups.
Conclusion: dietary lactic acid did not play any important role in development or progress of dental caries.

- ***Genetic Toxicity 'in Vitro'***

- Type: Ames test
System of testing: S. typhimurium strains TA97, TA98, TA100, TA104
Concentration: 0.5, 1.0, and 2.0 microliter lactic acid/plate
Metabolic activation: with and without
Result: negative
Type: Salmonella/microsome test (Ames test) and chromosomal aberration test in vitro
System of testing: reverse mutation assays, and Chinese hamster fibroblast cell line
Concentration: 10 mg/plate, resp. 1.0 mg/ml
Metabolic activation: without

Result: negative

- Type: Chinese hamster ovary K1 cells, chromosomal aberration tests, and the pH relationship of the medium and clastogenic activity was examined.
  System of testing: Cells were maintained in Ham's F12 medium, supplemented with 10% foetal calf serum.
  Concentration: 8-35 mM
  Cytotoxic Concentration: 14-35 mM, when pH was <= 5.8
  Metabolic activation: with and without
  Result:
  When the culture medium was first acidified by the lactic acid dose and then neutralised to pH 6.4 or when medium is containing 30 mM HEPES as buffer, lactic acid was non-clastogenic.
  Pseudo-positive reactions are seen as a result of non-physiological low pH.

- Type: review on several mutagenicity studies with lactic acid and some lactates.
  System of testing: various
  Concentration: various
  Metabolic activation: with and without
  Result: negative
  Result: the result of 11 studies is reviewed.

- ***Genetic Toxicity 'in Vivo'***

Due to the natural nature of L(+) lactic acid and the relative low contribution of "outside L(+) lactic acid" to the human metabolism, in vivo genotoxicity studies will not be required.

- ***Carcinogenicity***

- Species: rat
  Sex: male/female
  Strain: Fischer 344
  Administration: drinking water
  Exposure period: 2 years
  Frequency of treatment: daily, ad lib.
  Post exposure period: Autopsy on rats that died during study and those killed at the end. Examination macro-and microscopically for presence of non-neoplastic and neoplastic lesions
  Doses: 2.5 or 5 % Calcium lactate in the drinking water. Mean total Calcium lactate intake for males was 329.4 g, resp. 625.4 g; for females 237.7 g, resp. 412.1 g.
  Result: negative
  Control Group: yes, concurrent no treatment
  GLP: yes
  Test substance: The Calcium salt of lactic acid was tested
  Remark: Lactic acid tested as its Calcium salt. From this study the lactate intake is relevant, should be separated from the Calcium effects of a soluble Calcium salt.

- Species: rabbit
  Sex: female
  Administration: drinking water
  Exposure period: 5 or 13 months
  Frequency of treatment: twice daily
  Doses: 0.1-0.2 g/kg bw (5 months), and 0.1-0.7 g/kg bw (13 months)
  Result: negative
  Control Group: no data specified
  Result: No tumors were reported after 5 or 16 months. Further details not provided.

- ***Toxicity to Fertility***

The nature of the compound (part of human metabolism) does make toxicity studies to fertility not necessary

- ***Developmental Toxicity/Teratogenicity***

- Species: mouse
  Sex: female
  Strain: CD-1
  Administration: gavage
  Exposure period: gestational days 6-15
  Frequency of treatment: daily
  Duration of test: 10 days
  Doses: 570 mg/kg bw/day
  Control Group: yes, concurrent no treatment
  NOAEL Maternal Toxicity: >= 570 mg/kg bw
  NOAEL Teratogenicity: >= 570 ml/kg bw
  Result: Lactic acid was neither maternotoxic nor embryofetotoxic when given orally to mice at 570 mg/kg bw/day on gestation days 6-15.

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